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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Naweed MUHAMMAD et al.

Application No.: 10/823,426 Confirmation No.: 4034

Filed: April 12, 2004 Art Unit: 1618

For: METHODS AND COMPOSITIONS FOR ADMINISTRATION OF TRPV1 AGONISTS Examiner: M. Young

DECLARATION OF GEERTRUI F. VANHOVE UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I am currently Vice President of Clinical Research at NeurogesX in San Mateo, California, and have an M.D. and Ph.D. I have extensive experience in researching treatments for pain and have been working in this field for 4 years. My *curriculum vitae* is attached as Exhibit A.

The above mentioned application is concerned with liquid formulations and their use in the treatment of pain. Under my supervision, we have carried out the following clinical studies and made certain observations.

CLINICAL STUDY 1 – Comparison between liquid and patch formulations

We compared the effects of a liquid and patch formulation on epidermal nerve fiber density (ENF), while measuring pain and tolerability. The following treatments were studied:

- Formulation A: capsaicin **liquid** application (10% w/v capsaicin dermal liquid, 85% v/v propylene glycol, 15% v/v oleyl alcohol), exposure time 5, 15, or 25 minutes
- Formulation B: capsaicin **patch** (8% w/w capsaicin), exposure time 60 minutes
- Formulation C: control test article (100% v/v propylene glycol), exposure time 15 minutes.

Subjects were randomized into one of the six treatment sequence groups. Each subject received two Formulation A liquid applications for 5, 15 or 25 minutes at two sites on each anterior medial thigh, one 60-minute Formulation B patch application and one 15-minute control application.

ENF density after treatment with liquid or patch

Epidermal nerve fiber (ENF) density was measured 7 days after treatment. Significant reductions in ENF were observed for both Formulation A (liquid applied for 5, 15, or 25 minutes) and Formulation B (patch applied for 60 minutes), as summarized in Table 1. Observed ENF was reduced from 16.87 neuritis/mm in the control to 4.18 neurites/mm after 60 minutes with the patch. Treatment with the liquid formulation after only 5 minutes resulted in 4.70 neurites/mm.

Table 1. Summary of Epidermal Nerve Fiber Immunostaining at Week 1

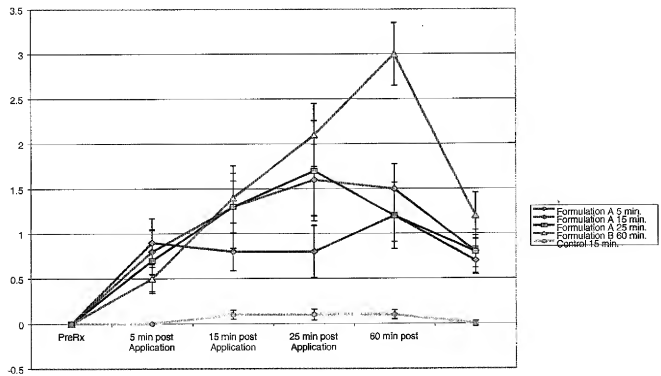
		Neurites/mm (Mean ± SD)	Ratio over control (Mean ± SD)
Treatment	**N**		
Formulation C (Control)	28	16.87 ± 6.23	-
Formulation A liquid (5 min)	18	4.70 ± 3.28	0.26 ± 0.159
Formulation A liquid (15 min)	19	3.19 ± 2.59	0.23 ± 0.202
Formulation A liquid (25 min)	17	3.84 ± 3.60	0.29 ± 0.310
Formulation B patch	28	4.18 ± 4.47	0.25 ± 0.218

Pain scale rating after treatment with liquid or patch

The Numeric Pain Rating Scale (NPRS) pain scores of patients treated with either the patch or liquid formulation was measured. The pain score of patients treated with the liquid Formulation A is similar to the patch formulation up to 15 minutes post application. However, after 25 minutes the subjects treated with the liquid formulation experience less pain than subjects treated with the patch formulation. Unexpectedly, at 60 minutes post application, the pain score for subjects treated with the liquid formulation is half of the score of patch wearing subjects even for liquid formulations applied to the subjects for 25 minutes. Figure 1, below, summarizes the Numeric Pain Rating Scale (NPRS) after a period of time after treatment with Formulations A, B or with placebo.

The combination of the ENF and pain scale data shows the unexpected and surprising result that even a 5-minute application of liquid formulation A produced a robust reduction of epidermal nerve fibers comparable to a 60-minute application of the patch formulation, and that this reduction occurred with less pain than produced by patch formulation B.

Figure 1. Summary of NPRS Pain Scores on the Treatment Day (mean ± SE)



CLINICAL STUDY 2 - Topical Liquid Capsaicin-Containing Formulations

We compared the effects of 3 topical liquid capsaicin-containing formulations and a control formulation on epidermal nerve fiber density (ENF), while measuring pain and tolerability. The formulations are summarized in Table 2.

Table 2. List of Ingredients in Formulations A, C, D and E

	Formulation A	Formulation D	Formulation E	Formulation C (placebo)
Material	**weight %**	**weight %**	**weight %**	**weight %**
Propylene Glycol	78.79	73.15	-	100.00
Oleyl alcohol	11.38	-	-	
Oleic acid	-	9.22	-	
Benzyl alcohol	-	7.84	-	
DGME[a]	-	-	89.93	
Capsaicin	9.83	9.79	10.07	0
TOTAL	100.00	100.00	100.00	100.00

[a] Diethylene Glycol Monoethyl Ether

Each formulation was applied to the skin of 20 human volunteers for 15 minutes. Endpoints included changes in epidermal nerve fiber (ENF) density at 7 days after treatment; this is a marker for capsaicin-mediated effects on the cutaneous sensory system. The greater the effect, the more likely pain relief will occur.

ENF density after treatment with the various capsaicin formulations

Table 3 summarizes the change in epidermal nerve fiber density for the 4 formulations. The percentage reductions in ENF density were 50% for both Formulation A and Formulation D, but only 6% for Formulation E. The reduction in ENF density was not accompanied by a change in thermal, mechanical sensation or tactile thresholds. These data show that particular combinations of skin penetration enhancers in comparison to other formulations will provide the desired clinical effect.

Table 3. Summary of Epidermal Nerve Fiber Immunostaining at Day 7

	Neurites/mm (Mean ± SD)	Ratio Over Placebo (Mean ± SD)
Formulation C (Placebo)	15.46 ± 4.20	-
Formulation A	7.60 ± 3.35	0.50 ± 0.22
Formulation D	7.58 ± 2.95	0.50 ± 0.17
Formulation E	14.18 ± 4.49	0.94 ± 0.25

Pain scale rating after treatment with the capsaicin formulations

Furthermore, the tolerability of the Formulations was assessed during the treatment by measuring pain and erythema. Table 4 summarizes the Numeric Pain Rating Scale (NPRS) results obtained after application and removal of the Formulations A, C, D and E. It was found that the efficacious formulations (A & D) produced no more pain and erythema than an ineffective formulation (E). Therefore, these data suggest that two formulations which include two penetration enhancers show a surprising ability to affect epidermal nerve fibers in a single 15-minute application while still being tolerable.

Table 4. Summary of NPRS Pain Scores on the Treatment Day

	Formulation A	Formulation D	Formulation E	Formulation C (Placebo)
	Mean ± SD			
5 min. after application	1.6 ± 1.8	1.8 ± 1.5	1.5 ± 1.8	0.1 ± 0.3
10 min. after application	2.2 ± 2.0	2.1 ± 1.8	1.7 ± 1.5	0.3 ± 0.6
15 min. after application	2.4 ± 2.4	2.1 ± 2.1	1.9 ± 1.8	0.5 ± 0.7
15 min. after removal	1.9 ± 2.1	2.6 ± 2.2	2.1 ± 2.1	0.1 ± 0.3
30 min. after removal	1.6 ± 2.0	1.8 ± 1.9	0.9 ± 1.5	0.1 ± 0.2
45 min. after removal	1.5 ± 1.9	1.7 ± 1.4	0.4 ± 0.8	0.1 ± 0.2
Maximum NPRS	2.8 ± 2.20	3.2 ± 2.04	3.2 ± 2.21	0.5 ± 0.69

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this _____13th____ day of December, 2010 at San Mateo, CA_____.
(city, state)

[signature] Geertrui F. Vanhove

Trudy (Geertrui Felicitas Alida) Vanhove, MD, PhD, MBA

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Summary of Qualifications

- Thirteen years of clinical drug development experience in phases I-IV in small to large pharmaceutical and biotechnology companies
- Excellent organizational skills with demonstrated leadership in multicenter and international project management
- Excellent research and analytical skills with strong problem solving and multi-tasking abilities
- Detail oriented and time-sensitive
- Excellent presentation skills
- Self starter, hands-on and entrepreneurial
- Therapeutic areas include pain, inflammation, anti-infectives, oncology, cardiology and dermatology
- Delivery methods include parenterals, tablets, gels and patches.
- Prepared and successfully filed several IND's, one MAA and one NDA

Professional Experience

NeurogesX (2/2010-present), San Mateo, CA: Vice President, Clinical Development

NeurogesX (12/2006-present), San Mateo, CA: Senior Director, Clinical Development

- Prepared and filed MAA for Qutenza (a high concentration capsaicin patch for neuropathic pain) and received approval
- Prepared and filed NDA for Qutenza-4010 and received approval
- Put a publication strategy in place and authored numerous abstracts and manuscripts
- Prepared training materials for MSLs
- Prepared and filed IND for a new formulation of capsaicin (NGX-1998)
- Medical monitor on two phase III trials, one phase II and two phase I trials
- Project team leader for the new formulation team (NGX-1998)
- Conducted due diligence for in-licensing candidates

GIMV (7/2005-12/2006), Belmont, CA: Senior Investment Manager
GIMV is an investment company based in Antwerp with investments in life sciences companies in the US. Duties included the following:

- Sourcing of deal flow for private equity investments in biotech companies in the US
- Building of local network that will generate such deal flow
- Conducting due diligence and investment/divestment processes of such investments
- Monitoring the performance of the investment portfolio
- Monitoring the general market evolutions for the biotech sector in the US

Independent Consultant (3/2005-6/2005)
Consulted for Arriva Pharmaceuticals to identify in-licensing candidates for COPD/asthma.

XOMA (US) LLC, Berkeley, CA (10/1998-3/2005): Medical Director, Clinical and New Product Evaluation

- Project team leader of multidisciplinary teams (10-15 people) to develop new compounds for cancer, acne, prevention of pneumonia in trauma and rheumatoid arthritis
- Designed and implemented clinical trials in cancer, rheumatoid arthritis, acne, cardiology and prevention of pneumonia/ARDS in trauma patients
- Lead scientific advisory boards
- Filed 2 IND's: ING-1 (anti-EpCAM antibody for cancer) and XMP.629 (a topical antimicrobial peptide for acne)
- Evaluated in-licensing opportunities and conducted due diligence
- Designed and implemented internal processes and screening criteria to assess new compounds and targets for development

Abbott Laboratories, Abbott Park, IL (1996 – 1998): Associate Director, Medical Affairs

- Designed and implemented clinical trials with antiretrovirals (Ritonavir) and antibiotics (Clarithromycin) in Europe, Thailand and Brazil
- Served as part of a team to develop new anti-HIV and new anticancer compounds, including Abbott's protease inhibitor, Kaletra
- Team leader for buccal adhesive testosterone tablet
- Provided regulatory support for marketed products, ex-US
- Provided marketing support for marketed products, ex-US, including presentations at international meetings, review of promotional materials, writing of scientific publications, training of marketing personnel, pharmacovigilance

Education

St. Mary's College, Moraga, CA (January 2002 – June 2003)
Executive MBA program: Graduated with Honors

Stanford University, Stanford, CA (1994-1996)
Fellowship in Clinical Pharmacology (Supervisor: Prof. Terrence Blaschke)

- Designed pharmacokinetic studies
- Modeled pharmacokinetics of anti-HIV drugs in combination therapy
- Explored the relationship of antiviral drug exposure and drug response using modeling techniques
- Modeled and monitored drug compliance and response in HIV positive patients

Katholieke Universiteit Leuven, Leuven, Belgium (1990-1994)
PhD in Pharmacology (Advisor: Prof. G.P. Mannaerts)

- Dissertation: The peroxisomal ß-oxidation of 2-methyl-branched fatty acids
- Demonstrated that 2-methyl-branched fatty acids are predominantly oxidized by peroxisomes
- Purified the enzyme responsible for the first step of the peroxisomal ß-oxidation of 2-methyl-branched fatty acids from rat and human liver

Katholieke Universiteit Leuven, Leuven, Belgium (1983-1990)
MD: Graduated summa cum laude

Awards & Fellowships

- Belgian National Science Foundation Fellowship, 1990-1994
- Honorary Fulbright Scholarship 1994-1995
- Collen Research Foundation Fellowship, 1994-1996
- NATO Research Foundation Fellowship, 1994
- Rotary Foundation Fellowship, 1994
- Scholarship of the Flemish Community to study Spanish in Spain, 1986

Miscellaneous

- US citizen
- Fluent in English, French, and Dutch. Proficient in Spanish and German.

Patents and Publications

1. Methods and Material including for Treating Acne Related Applications, US patent application filed July 23, 2004. Lewis H. Lambert Junior and **Geertrui F. Vanhove**.
2. **Vanhove G**, Van Veldhoven PP, Vanhoutte F, Parmentier G, Eyssen HJ and Mannaerts GP (1991). Mitochondrial and Peroxisomal ß-oxidation of the Branched Chain Fatty Acid 2-Methylpalmitate in Rat Liver. *J. Biol. Chem.* 266, 24670-24675.
3. Van Veldhoven PP, **Vanhove G**, Vanhoutte F, Dacremont G, Parmentier G, Eyssen HJ and Mannaerts, GP (1991). Identification and Purification of a Peroxisomal Branched Chain Fatty Acyl-CoA Oxidase. *J. Biol. Chem.* 266, 24676-24683.
4. Van Veldhoven PP, **Vanhove G**, Asselberghs S, Eyssen HJ and Mannaerts GP (1992). Substrate Specificities of Rat Liver Peroxisomal Acyl-CoA Oxidases: Palmitoyl-CoA Oxidase, Pristanoyl-CoA Oxidase and Trihydroxycoprostanoyl-CoA Oxidase. *J. Biol. Chem.* 267, 20065-20074.
5. **Vanhove G**, Van Veldhoven PP, Eyssen HJ and Mannaerts GP (1993). Mitochondrial Short Chain Acyl-CoA Dehydrogenase of Human Liver and Kidney can function as an Oxidase. *Biochem. J.* 292, 23-30.
6. **Vanhove GF**, Van Veldhoven PP, Fransen M, Denis S, Eyssen HJ, Wanders RJA and Mannaerts GP (1993). The CoA esters of 2-Methyl Branched Chain Fatty Acids and of the Bile Acid Intermediates Di- and Trihydroxycoprostanic Acids are Oxidized by one Single Peroxisomal Branched Chain Acyl-CoA Oxidase in Human Liver and Kidney. *J. Biol. Chem.* 268, 10335-10344.
7. Vanhole C, de Zegher F, Casaer P, Devlieger H, Wanders RJA, **Vanhove G** and Jaeken J (1994). A new Peroxisomal Disorder with Fetal and Neonatal Adrenal Insufficiency. *Arch. Dis. Child.* 71, F55-F56.
8. Novikov KD, **Vanhove GF**, Carchon H, Asselberghs S, Eyssen HJ, Van Veldhoven PP and Mannaerts GP (1994). Peroxisomal ß-oxidation: Purification of four novel 3-hydroxyacyl-CoA dehydrogenases from rat liver peroxisomes *J. Biol. Chem.* 269, 27125-27135.
9. **Vanhove G** (1994). The peroxisomal β-oxidation of 2-methyl-substituted fatty acids, Ph. D. Thesis. *Acta Biomedica Lovaniensia* 75 (Leuven University Press).
10. **Vanhove GF**, Schapiro JM, Winters MA, Merigan TC and Blaschke TF (1996). Compliance and drug failure in protease inhibitor monotherapy. *JAMA* 276 (24): 1955-1956.
11. **Vanhove GF**, Kastrissios H, Gries JM, Verotta D, Park K, Collier AC, Squires K, Sheiner LB and Blaschke TF (1997). Pharmacokinetics of saquinavir, zidovudine and zalcitabine in combination therapy. *Antimicrobial Agents and Chemotherapy* 41(11): 2428-2432.
12. **Vanhove GF**, Gries JM, Verotta D, Sheiner LB, Coombs R, Collier AC and Blaschke TF (1997). Exposure-response relationships for saquinavir, zidovudine and zalcitabine in combination therapy. *Antimicrobial Agents and Chemotherapy* 41(11): 2433-2438.
13. MacLeod CM, Schotzinger RJ, **Vanhove GF** and Bachand RT (1999). Pharmacokinetics and safety of a once-daily clarithromycin formulation. *Advances in Therapy* 16(1) : 1-12
14. de Bono JS, Tolcher AW, Forero A, **Vanhove GFA,** Takimoto C, Bauer RJ, Hammond LA, Patnaik A, White ML, Shen S, Khazaeli MB, Rowinsky EK, and LoBuglio A (2004). Pharmacokinetics, Tolerability, and Biodistribution of ING-1, a Human-Engineered ™ Monoclonal Antibody to Ep-CAM in Patients with Advanced Adenocarcinomas. *Clin. Cancer Res.* 10(22):7555-65.
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21. Backonja MM, MD, Malan TP, **Vanhove GF** and Tobias JK for the C102/106 Study Group NGX-4010 (2010). A High-Concentration Capsaicin Patch, for the Treatment of Postherpetic Neuralgia: A Randomized, Double-Blind, Controlled Study with an Open-Label Extension. *Pain Medicine.* Apr;11(4):600-8.
22. Webster LR, Tark M, Rauck R, Tobias JK and **Vanhove GF** (2010). Effect of duration of postherpetic neuralgia on efficacy analyses in a multicenter, randomized, controlled study of NGX-4010, an 8% capsaicin patch evaluated for the treatment of postherpetic neuralgia. *BMC Neurology* Oct 11;10:92.
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24. Webster LR, Peppin JF, Murphy FT, Lu B, Tobias JK and **Vanhove GF** (2010). Preliminary Efficacy, Safety and Tolerability of NGX-4010, Capsaicin 8% Patch, in Patients with Peripheral Neuropathic Pain. *Diabetes Research and Clinical Care.* Submitted for publication.
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